IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

GELFAND et al.

Serial No.: 09/809,753

Filed: March 14, 2001

Atty. File No.: 2879-74

For: "METHOD FOR REDUCING ALLERGEN-INDUCED AIRWAY HYPERRESPONSIVENESS"

Group Art Unit: 1644

Examiner: Huynh, Phuong N.

DECLARATION OF ERWIN W. GELFAND AND AZZEDDINE DAKHAMA (Under 37 CFR 1.131)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Dear Sir:

We, Erwin W. Gelfand and Azzeddine Dakhama, each declare as follows:

1. I am a co-inventor of the above-referenced patent application and am familiar with the application.

2. This Declaration under 37 CFR 1.131 is being submitted in conjunction with a Response to an Office Action mailed on August 10, 2005, filed on this same date.

3. This Declaration provides factual evidence that the invention as claimed in the above-identified patent application was reduced to practice prior to the earliest priority date of December 24, 1999 of U.S. Patent No. 6,743,429 by Cadieux, filed in the United States on December 30, 1999, which published as Publication No. 2002/0037846A1 on March 28, 2002 and which issued on June 1, 2004. All acts relied upon to establish the dates of actual reduction to practice were carried out in the United States.

Evidence of Actual Reduction To Practice

The invention presently claimed in the above-identified patent application was reduced to practice prior to December 24, 1999, which is the earliest priority date for U.S. Patent No. 6,743,429. As evidence of actual reduction to practice by a date prior to

December 24, 1999, enclosed as Exhibit A and Exhibit B are a notebook page and a data table and figure from two experiments that were completed by the inventors prior to December 24, 1999. These experiments demonstrate that administration of calcitonin gene related peptide (CGRP) to a mammal inhibits allergen-induced airway hyperresponsiveness (AHR) in the mammal.

Specifically, in the first experiment, referring to first to Exhibit A, mice were sensitized by intraperitoneal injection of an allergen (i.e., ovalbumin) and were then exposed by inhalation to a nebulized amount of the allergen (ovalbumin) that is sufficient to induce airway hyperresponsiveness (AHR) in the mice in the absence of treatment with CGRP (see the designation of "OVA ipNeb" on page A). Control mice received nebulized allergen (ovalbumin) only (see the designation of "OVA Neb" on page A). One group of mice receiving the intraperitoneal ovalbumin sensitization and nebulized ovalbumin challenge was treated by intraperitoneal administration of CGRP before the challenge (see the designation of "OVA ipNeb/CGRP ip x3" on page A). Airway function was assessed *in vivo* by measuring changes in lung resistance (R_L) in response to intratracheal challenge with aerosolized methacholine at doses of 1.56, 3.12, 6.25, 12.5 and 25 mg/ml in saline as indicated in Exhibit A. In addition, recovered BAL fluids were examined for cellular composition as shown in the table in Exhibit A. At the bottom of Exhibit A, the experimental results conclude that the treatment with CGRP had no effect on eosinophils in the BAL fluid and that the treatment inhibited AHR.

The table shown on page 1 of Exhibit B contains the results from a study similar to that described in Exhibit A and shows that CGRP has an inhibitory effect on ovalbumin-induced airway hyperresponsiveness. The data are tabulated as follows:

> Column 1 shows the increasing doses in mg/ml of aerosolized methacholine (Mch) which was administered intratracheally to mice to measure airway hyperresponsiveness.
>
> Columns 2 and 3 show the mean and standard error, respectively, of the changes in lung resistance in response to each dose of methacholine for ovalbumin-sensitized and challenged mice (OVA). The changes are

presented as percent increases from baseline values recorded after intratracheal administration of aerosolized saline (no methacholine).

Columns 4 and 5 show the mean and standard error, respectively, of the changes in lung resistance in response to each dose of methacholine for ovalbumin-sensitized and challenged mice that were treated with CGRP (OVA+CG). The changes are presented as percent increases from baseline values recorded after intratracheal administration of aerosolized saline (no methacholine).

Columns 6 and 7 show the mean and standard error, respectively, of the changes in lung resistance in response to each dose of methacholine for ovalbumin-sensitized and challenged mice that were treated first with a CGRP antagonist (CGRP8-37) followed by CGRP (OVA+Antagonist+CG). The changes are presented as percent increases from baseline values recorded after intratracheal administration of aerosolized saline (no methacholine).

Columns 8 and 9 show the mean and standard error, respectively, of the changes in lung resistance in response to each dose of methacholine for non-sensitized control mice (PBS). The changes are presented as percent increases from baseline values recorded after intratracheal administration of aerosolized saline (no methacholine).

The Figure shown on page 2 of Exhibit B was produced from the data described on page 1 of Exhibit B and illustrates the results of the study, that CGRP inhibits OVA-induced airway hyperresponsiveness to methacholine.

These experiments, which were performed and completed prior to December 24, 1999, therefore demonstrate that the claimed method of the present invention operated for its intended purpose (i.e., administration of CGRP to a mammal inhibits airway hyperresponsiveness in the mammal).

This factual evidence is believed to be sufficient to establish an actual reduction to practice of the claimed invention at a date prior to December 24, 1999.

4. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

2.7.06
Date

Erwin W. Gelfand

02-07-06
Date

Azzeddine Dakhama

Dry conc on OVA / Bruxes

Sigma to get ~10^{-7} M in vivo
[illegible] ~ 2 [illegible] [illegible]
Give 20μl (1:100) from stock 10^{-5} M

OVA [illegible]
OVA ipNeb
OVA ipNeb / CCHP ip x3 (before each challenge).

MCh response ~~50~~, 25, 12.5, 6.25, 3.125, 1.56 - SA

BAL count:	Total (10^3)	% MAC	EOS	LYM	NEU
2MAR99/1	70	99	—	—	1
— 2	68	97	—	1	2
— 3	75	98	1	—	1
— 4	92	96	1	1	2
— 5	254	54	40	4	2
— 6	286	62	34	3	1
— 7	315	48	41	7	4
— 8	235	67	27	6	—
— 9	246	52	44	1	3
— 10	380	43	54	2	1
— 11	215	61	35	3	1
— 12	270	47	40	2	1

→ No effect on EOS
→ Some [illegible] on AHR ([illegible])

EXHIBIT A

[redacted]

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AHR/RL X±SEM

	1	2	3	4	5	6	7	8	9
	Dose of MCh	OVA	SD1	OVA+CG	SD2	OVA+Ant+CG	SD3	PBS	SD
1	0	100	0	100	0	100	0	100	0
2	1.56	137	1.5	109	1.1	129	8	120	2
3	3.12	257	22	134	7	253	32	176	18
4	6.25	456	37	186	5	491	104	260	42
5	12.5	632	16	244	30	603	48	277	34

EXHIBIT B pg.1

Effect of CGRP on OVA-induced AHR to MCh